APPENDIX 4

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF OHIO
WESTERN DIVISION

J.B.D.L. Corp., d/b/a Beckett Apothecary, et al., Plaintiffs,	Case No. C-1-01-704
vs.	
Wyeth-Ayerst Laboratories, Inc., et al., Defendants.	

EXPERT REPORT OF PHILIP M. SARREL, M.D.

I. Qualifications

1. I am an Emeritus Professor of Obstetrics and Gynecology and Psychiatry at Yale University, where I have been training medical students and residents in the areas of obstetrics, gynecology and psychiatry for 41 years. From 1973 - 1978, I was Director of Student Medicine for Yale students during their training in obstetrics and gynecology. Throughout my career, I have provided training to residents and medical students in the medical issues confronting women during menopause and the use of hormone replacement therapy to treat conditions associated with the menopause.

2. Additionally, I am an Attending Physician in Internal Medicine at the Yale-Griffin Center in Derby, Connecticut, where I serve as a research associate in the Center for Preventive Medicine. I also am Director of the Yale Sex Counseling Program in the Department of Psychiatry at Yale University Health Services.

3. I am Board Certified in Obstetrics and Gynecology.

4. I retired from full-time practice in July 2002, and continue to see patients on a part-time basis.

5. I am a founding member of the International Menopause Society and the North American Menopause Society. I currently serve as an editor of the organizations' journals, which are called respectively Maturitas and Menopause: The Journal of the North American Menopause Society. I am also an editor of the Journal of the Dutch Menopause Society and the Journal of Gender Specific Medicine. Additionally, I review, or "referee", articles concerning hormones and cardiovascular, sexual and/or psychiatric function for several medical journals, including the American Journal of Obstetrics and Gynecology and the Journal of Clinical Endocrinology and Metabolism, and Fertility and Sterility. I have co-edited three medical textbooks on menopause-related issues and studies.

6. In 1976, I founded the Yale Menopause Program. The Program employs an interdisciplinary approach, bringing together physicians and nurses from numerous specialty areas, including cardiology, neurology, psychology, epidemiology, dermatology and gynecology, as well as nutritionists. The over-arching goal of the Program is to develop an understanding of menopause and hormone treatment as they affect a woman's capacity to function at home and in the workplace. Over the years, I have evaluated, treated and monitored the effects of hormone therapy in more than 1600 women, some of whom have had as many as 35 years of follow-up care.

7. As a member of the academic faculty of the Yale School of Medicine, my research primarily has been funded since 1976 by the National Institutes of Health, and has focused on the role of ovarian hormones in the nervous and cardiovascular systems. My publications (listed

in my Curriculum Vitae, attached as Exh. A) present data about the effects of menopause and hormone replacement on psychosexual function and circulatory disorders, such as heart attacks and stroke.

8. In sum, my career has been dedicated to understanding the major medical and psycho-social issues confronting women in mid-life and beyond; the development of optimal hormone replacement in menopausal women, and the viability of alternative therapies, such as dietary programs and herbal preparations. A complete summary of my education, professional experience and publications is outlined in my Curriculum Vitae.

II. Assignment

9. I have been asked by plaintiffs to serve as an expert on menopausal health issues and the provision of optimal menopause-related hormone treatments and, specifically, to opine on the following:

(1) the changes of the menopause and their significance in a woman's life;

(2) the goals of optimal hormone replacement therapy;

(3) the problems associated with the use of conjugated equine estrogens, *i.e.*, Premarin;

(4) the advantages of Cenestin, a newer, more technologically advanced hormone replacement product; and

(5) the significance of formulary obstacles to optimal treatment.

III. Compensation and Documents Reviewed

10. I am being compensated at the rate of $500.00 per hour.

11. In preparing this report, I primarily have relied on my 41 years of researching, teaching, and treating the symptoms and conditions associated with menopause. A listing of materials I reviewed in connection with my work on this matter is attached as Exh.B.

IV. Menopause

12. Basically, menopause marks the end of the reproductive phase of a woman's life. During the menopause process, the ovaries essentially run out of egg cells and those cells associated with the monthly development of an egg. During a woman's reproductive years, these latter cells take cholesterol from the blood stream and convert it into hormones known as estrogens, progesterone, and androgens.

13. These hormones are directly released into the blood's circulatory system, entering cells throughout the body. Within each cell, the hormone attaches to a specific protein called a "hormone receptor." Thus there are "estrogen receptors," "progesterone receptors" and "androgen receptors." When activated, this hormone and hormone-receptor combination enables the stimulation of genes that in turn control cell structure and function. The effects are numerous and varied, and contribute significantly to the life processes of the whole body. For example, estrogens are known to stimulate more than 400 cellular actions that affect structure and function throughout the body, including the brain, bone, blood circulation, and genital tissues such as those lining the vagina and the uterus.

14. Menopause is the time when the ovaries lose the cells involved in reproduction and hormone production. Menopause-induced hormone depletion causes many, if not most, women to develop symptoms and presents a risk as well for certain medical conditions. The most

common medical conditions related to ovarian hormone deficiency include osteoporosis, which can lead to bone fracture, heart disease and stroke. (These are further discussed below.)

15. It is estimated that at least 50% of women develop severe menopause-related symptoms, which persist for a sizeable minority of women for ten or more years. The most severe symptoms occur with abrupt hormone withdrawal. For example, if the uterus and ovaries are surgically removed and no hormone replacement is given, most women within the next few days will develop severe hot flushes, reflecting the effects of hormone depletion throughout the entire circulatory system. (In some women these reactions are triggered within the first 24 hours following surgery.) Women may suffer chest pressure and irregular heart rates, severe headaches, sleep disruption and psychological depression in conjunction with these hot flushes. Sudden hormone withdrawal, even when the uterus and ovaries are intact, also is associated with migraine attacks, vaginal bleeding and even, as more recently recognized, heart attacks.

V. Treating the Symptoms and Conditions of Menopause

16. The effective treatment of menopausal symptoms has been and continues to be the primary goal of postmenopausal hormone replacement therapies. Relief from these symptoms is the main reason most women seek professional help, and these symptoms are the treatment indications for hormone replacement drugs recognized by the Food and Drug Administration (FDA).

17. To be effective, hormone replacement therapy must first help a woman to eliminate or reduce her symptoms to a manageable level. Most doctors consider treatment to be effective when it eliminates or reduces symptoms such that they no longer interfere with a woman's capacity to function at home or in the workplace.

18. Doctors also seek to avoid or minimize the adverse effects of hormone replacement therapy, including breast tenderness, headaches and irregular bleeding. Treatment with estrogen alone increases the risk of cancer of the lining of the uterus, but this increased risk is virtually eliminated when another hormone, a progestogen, is added to estrogen. The term progestogen is used to encompass the hormone progesterone and a variety of hormones derived from the progesterone molecule. However, certain progestogens, such as medroxyprogesterone acetate (MPA)– which is used in the Wyeth product Prempro – have been associated with an increased risk in breast cancer.[1] Doctors must consider all of these factors when determining the best course of treatment for a patient experiencing menopausal symptoms.

VI. **A Comparison of Premarin and Cenestin**

19. I believe that most doctors keep an open my mind when considering hormone treatments for menopausal symptoms and menopause-related disease prevention. However, in selecting a hormone replacement therapy, physicians naturally would prefer to use a product which (1) has been subjected to the FDA's modern and more rigorous approval process; (2) contains few, if any, contaminants; (3) does not vary from pill to pill and maintains relatively stable drug-blood levels around the clock; (4) complies with FDA standards for dissolution and

[1] The Women's Health Initiative (WHI) in July 2002 stopped its placebo-controlled clinical trial of the risk and benefits of combined estrogen and progestogen (Premarin and Prempro (Premarin combined with MPA)) in healthy menopausal women due to an increased risk of breast cancer, as well as increased risks for coronary heart disease, stroke, and pulmonary embolism. There was also reported fewer incidents of hip fractures and colon cancer. In March 2004, the WHI directed women participating in the estrogen-alone portion of the trial, who were taking Premarin or placebo, to stop taking their study pills, after finding that estrogen alone provides no protection against heart disease, a key question of the study. Premarin also appeared to increase the risk of stroke, while decreasing the risk of hip fracture. These studies will be further discussed below.

absorption; and (5) otherwise effectively treats the primary symptoms associated with hormone depletion (*i.e.*, hot flushes, night sweats and vaginal atrophy.)

20. It is my opinion, which is based on my extensive experience in the menopause field, that Cenestin comes much closer than Premarin to meeting doctors' criteria for a safe and effective hormone replacement therapy.

21. Both Premarin and Cenestin are estrogen replacement therapies (ERTs), used to treat women who have undergone hysterectomies. Premarin has been by far the most widely used ERT since it was approved by the FDA in 1942. I believe, however, that, when compared to Cenestin, Premarin's current predominance in the conjugated estrogen field largely has been due to its success in securing favorable placement on various health care formularies, rather than because of any superior safety or efficacy.

22. Premarin is derived from pregnant mares' urine. It contains 10 different horse estrogens, which account for the drug's estrogenic effects in menopausal women. These horse estrogens are "conjugated" estrogens, meaning that each is an estrogenic steroid to which another chemical is attached. (These 10 estrogens have been well-documented in the medical literature.) As discussed below, Premarin also contains other steroids, as well as hundreds of horse urine by-products, such as creosote, many of which remain unknown.

23. Cenestin is a synthetic conjugated estrogen. It contains nine of the key estrogenic substances contained in Premarin. These nine estrogens have been determined to account for 98 percent of the estrogen effects of Premarin. However, Cenestin does not contain any of the horse urine by-product contaminants in Premarin. The ratios of the conjugated estrogens in Cenestin also duplicate those of Premarin's conjugated estrogens. Because estrogens vary in potency,

resulting in different cellular effects, replication of the concentrations of the hormones in Premarin was deemed essential in the development of Cenestin. Furthermore, Cenestin is available in the most commonly prescribed dosages of Premarin.

A. Premarin was never subjected to the FDA's modern approval process.

24. Premarin was approved by the FDA in 1942, decades before the agency had established the rigorous approval process, including new drug dissolution requirements, that is in place today. In my experience, most doctors prefer to prescribe drug products that meet current FDA standards. In fact, it is hard to think of a 60-year-old drug - other than aspirin and digoxin - that is still in common use.

B. Premarin has not been fully characterized.

25. In 1942, drugs were not required to be fully characterized, *i.e.* to have identified all biologically active elements and the percent of drug content taken up by each of these elements. Wyeth, at the FDA's request, since has attempted to fully characterize Premarin, and to date has identified 250 chemicals that are contained in the drug. However, it is my understanding that up to 25 percent of the contents in a typical Premarin tablet remain unknown.

26. Today, to obtain FDA approval, a drug must be fully characterized. Cenestin, which was approved by the FDA in March 1999, meets that requirement. Unsurprisingly, physicians prefer to work with drugs whose contents are fully known, and in which non-essential components – such as the chemicals and other substances found in Premarin – have been eliminated. Because almost all modern menopause drugs, including Cenestin, are so-called "clean" hormones and Premarin is not, these drugs in my opinion offer a significant advantage over Premarin.

C. Variability

27. Another disadvantage of Premarin is that the contents of individual tablets vary, since batches of horse urine contain different levels of hormones, varying from one pregnant mare's urine to another. This presents a problem for physicians and their patients, since it is impossible to tell whether each pill contains the appropriate amount of estrogen for an individual woman's needs. As with improper dissolution and absorption (discussed below), these uneven estrogen levels can result in the persistence of symptoms and, ultimately, the frustrated abandonment of treatment, rather than the search for a more effective therapy.

28. Because it is a synthetic product and each tablet is made exactly the same way, Cenestin contains identifiable and consistent quantities of essential estrogens, eliminating the issue of content variability.

D. Dissolution and absorption of Premarin tablets is not uniform.

29. The manner in which a drug dissolves and is absorbed is an important factor in achieving optimal hormone replacement therapy, and is a significant consideration for most doctors in treatment selection. Poor dissolution and absorption can cause patients to experience fluctuating highs and lows in estrogen levels, resulting – as with content variability – in the persistence of symptoms and the eventual abandonment of treatment.

30. Different tablets prescribed as hormone replacement therapy also have different coatings, which affect delivery of the drug into the blood stream, since the coating has to dissolve to release the hormone. Premarin is coated with "pharmaceutical glaze", a euphemism for shellac[2], a substance that is not readily dissolved or absorbed by many women. Modern oral hormone

[2] It is my understanding that shellac is constituted of ground-up beetle wings.

replacement drugs, like Cenestin, use a film coating that is readily dissolved, thus enabling release of the hormone(s).[3]

31. Various dissolution tests have shown that when Premarin is ingested, the estrogens that are released have peak levels and then dip into a trough in the course of 24 hours.[4] If the hormone is not released regularly, it is not surprising to find that symptoms persist or that new symptoms are generated.[5]

32. In fact, the failure of Premarin tablets to meet FDA dissolution standards has resulted in the recall of hundreds of millions of Premarin tablets over the past four years, with the most recent recall occurring in March 2004.

33. In addition to symptom persistence, variability in dissolution and absorption is also problematic because products that maintain relatively stable serum levels are believed to have the least side effects. Side effects of hormone withdrawal include sleep disturbance, persistent hot flushes, and headaches. Factors that affect the stability of the serum estrogen level include purity of the product, consistency of the components, and controlled delivery of the hormones.

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[3] *See*, Hess H.M., Dowling T.C., Schwartz M.J., *Clinical Implications of the Differences in Dissolution and Absorption Characteristics of Oral Estrogen Therapy Agents*, The Journal of New Developments in Clinical Medicine 2003; 21:85-95. (Stomach acidity also plays a role in facilitating the digestion of shellac-coated products, as stomach acid is necessary to dissolve the coating. (When inadequate stomach acid is produced, a common condition in an aging population, or antacid medication is taken, dissolution is affected and drug products contained in a shellac coating may not be absorbed. By contrast, the newer film coatings - such as the coating used on Cenestin tablets - are able to dissolve more readily in a less acidic stomach environment, thereby insuring more consistent dissolution and absorption.)

[4] *Id.*

[5] *See*, MacLennan A., Lester S., Moore V., *Oral oestrogen replacement therapy versus placebo for hot flushes*, Cochrane Review, Cochrane Database Syst. Rev. 2001:1:CD002978; MacLennan A., Lester S., Moore V., *Oral estrogen replacement therapy versus placebo for hot flushes: a systematic review*, Climateric 2001; 4:458-74.

34. To my knowledge Cenestin has not experienced any such dissolution failures. Duramed's internal dissolution tests also have confirmed that Cenestin offers a distinct advantage over Premarin in the area of dissolution and absorption.[6]

E. Premarin fails to alleviate symptoms in a percentage of the patient population.

35. It is estimated that more than 25 percent of women prematurely discontinue treatment within the first three months after beginning hormone replacement therapy, citing the adverse effects and/or ineffectiveness of treatment.[7]

36. In fact, studies have shown that between 20-50 percent of women continue to experience symptoms while on Premarin.[8] Hot flushes, for example, persist in a sizeable minority (about 25%) of women who use Premarin at ostensibly therapeutic dose levels. Breakthrough bleeding, breast tenderness and headaches are also among the symptoms women experience while taking Premarin and Prempro. (Headache in particular has been related to highs and lows in serum

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[6] *See,* Hess H.M., Dowling T.C., Schwartz M.J., *Clinical Implications of the Differences in Dissolution and Absorption Characteristics of Oral Estrogen Therapy Agents,* The Journal of New Developments in Clinical Medicine 2003; 21:85-95.

[7] *Id.; see also,* Schiff I., Rebar R., Cramer J., et al., *Achieving Long-Term Continuance of Menopausal ERT/HRT: Consensus Opinion of the North American Menopause Society,* Menopause 1998; 5:69-76. (I also was one of the authors of the consensus statement.)

[8] *See,* Burger H.G., Hailes J., Menelaus M., et al., *The management of persistent menopausal symptom with oestradiol-testosterone implants: clinical, lipid and hormonal results,* Maturitas 1984; 6:351-58 (the authors conclude that among women using the 1.25 mg. dose of Premarin who have persistent hot flushes "... it suggests that symptoms are related to therapy rather than absolute hormone concentrations"); Campbell S.J. and Whitehead M., *Oestrogen therapy and menopause syndrome,* Clin Obstet Gynecol 1977, 4:31-47 (improvement in hot flushes observed in only 40-50 percent of women in study using 1.25 mg. Premarin); MacLennan A., Lester S., Moore V., *Oral oestrogen replacement therapy versus placebo for hot flushes,* Cochrane Review, Cochrane Database Syst. Rev. 2001:1:CD002978; MacLennan A., Lester S., Moore V., *Oral estrogen replacement therapy versus placebo for hot flushes: a systematic review,* Climateric 2001; 4:458-74; Hays J., Ockene J.K., Brunner R.L., et al., *Effects of estrogen plus progestin on health-related quality of life,* New Engl. J. Med. 2003 May 8; 348 (19):1839-54.

estrogen levels, as has breakthrough bleeding.) A typical scenario in an inadequately treated woman is to ingest the drug first thing in the morning, feel well most of the day, but to then awaken at night, about 16 to 20 hours after ingestion, with hot flushes, reflecting depletion of the hormone. Women who experience such adverse effects often will stop treatment and subsequently disappear from physicians' practices.

37. These were the findings in the national study that I designed and supervised in 1998 to evaluate women's rationales for discontinuance of hormone replacement therapy. The study, in which virtually all participants were taking Prempro or Premarin, essentially found that the younger women, those within two years of their natural menopause, stopped treatment because they feared breast cancer. Women who were two or more years past their last menstrual flow cited adverse effects and persistent symptoms, including irregular bleeding, headache, psychological depression, persistent hot flushes and sleep disturbance, as reasons for discontinuing therapy. The findings were presented to the annual meeting of the North American Menopause Society (NAMS) and were integrated in a consensus statement[9] published by the Society.

38. It therefore is vitally important that women be provided a hormone replacement therapy that both is as safe as possible and successfully eliminates symptoms. Significantly, my clinical experience and the experience of other practitioners I know is that many of the women who remained symptomatic on Premarin improve when they switch to Cenestin.[10]

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[9] *See*, Sarrel P.M., Giblin K., Liu X, *Health care delivery and HRT experience effects on HRT continuance*, North American Menopause Society, Austin, Sept. 5-6 1997; Schiff I., Rebar R., Cramer J., et al., *Achieving Long-Term Continuance of Menopausal ERT/HRT: Consensus Opinion of the North American Menopause Society*, Menopause 1998; 5:69-76.

[10] *See*, Hess H.M., Dowling T.C., Schwartz M.J., *Clinical Implications of the Differences in Dissolution and Absorption Characteristics of Oral Estrogen Therapy Agents*, The Journal of

F. Lowest dose recommended.

39. Since the WHI reported an increased risk of breast cancer in women using Prempro, the FDA has advocated the use of the lowest effective doses of estrogens. Optimal use therefore would be the 0.3mg or 0.45mg doses of Premarin or Cenestin, and both drugs in these doses have been approved by the FDA for control of hot flushes. Nevertheless, this dose of Premarin does not appear to be optimal for many women judging by the number of 0.9 and 1.25mg dose Premarin prescriptions in current use, as evidenced by statistics reported by IMS in 2002..

G. Premarin is not effective for the treatment for osteoporosis.

40. Both Cenestin and Premarin have been approved for vasomotor systems (*e.g.* hot flushes and night sweats), the symptoms for which most women seek professional help.

41. However, Premarin, but not Cenestin, also has an FDA indication for osteoporosis prevention; this indication often has been cited by Wyeth as one of the reasons women should choose Premarin to treat their menopausal symptoms. I believe, as do many other doctors with whom I've spoken, that this osteoporosis indication is unimportant, since (1) current recommendations are that hormone replacement therapy should be for as short a duration as possible, (2) most women use hormone replacements no more than a few years, (3) the prevention of osteoporosis necessarily requires long-term treatment and (4) alternative non-estrogenic drugs for osteoporosis prevention and treatment have gained considerably in use since issuance of the findings of the WHI report.

42. Most studies indicate that the majority of women do not use hormone therapy long enough to provide substantial osteoporosis benefits. For example, the NAMS study reported

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New Developments in Clinical Medicine 2003; 21:85-95.

that only 8 to 12 percent of women use postmenopausal hormones for more than two years.[11] I believe most authorities in this field would agree that that is not enough time to achieve long-term benefit.[12]

43. Both the leading professional organizations and the FDA indicate that women should not use estrogens for preventing osteoporosis but should choose treatments designed specifically to prevent the condition. Most recently, the WHI study found that hormone therapy for the prevention of postmenopausal osteoporosis should only be considered for those women at significant risk for the disease who are unable to take non-estrogen medications.

44. As indicated above, most women seeking hormone replacement treatment do so to alleviate symptoms such as hot flushes, night sweats and vaginal atrophy, and the first priority of doctors in treating these patients is to alleviate these symptoms. Treatment of other conditions such as osteoporosis is of secondary concern.[13]

45. Additionally, most doctors are aware that any osteoporosis benefit from Premarin and other hormone replacement therapies are believed to be a "class effect" of estrogens. Thus, even though Cenestin is not indicated for treatment of osteoporosis, most doctors believe patients on Cenestin will receive the same osteoporosis benefits as would be achieved on Premarin.

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[11] *See*, Schiff I., Rebar R., Cramer J., et al., *Achieving Long-Term Continuance of Menopausal ERT/HRT: Consensus Opinion of the North American Menopause Society*, Menopause 1998; 5: 69-76.

[12] *See e.g.*, Liu J.H., *Pharmacological interventions for reducing fracture risk*, Menopause Management 2003 March/April: 13 (Suppl. 1) 35-38.

[13] *See*, Hammond C., Blohm P.L., *Pharmacological background of estrogen replacement therapy and continuance, Estrogens and Progesterones in Clinical Practice* (London 1998), p. 663. (Research at Duke University indicates that in addressing hormone replacement treatment with patients, 84% of doctors focused on the short-term effects of hormonal treatment (*e.g.*, alleviation of hot flushes and night sweats) and did not address long-term health risks such as osteoporosis.)

H. The benefits of Premarin have not been definitively established.

46. In the 1982-1983 academic year, I spent a sabbatical leave at King's College Hospital in London, England where I worked full time in the menopause clinic. The clinic, headed by Dr. Malcolm Whitehead, was and I believe continues to be one of the world's outstanding centers for menopause healthcare and research. During that time, I treated and monitored effects of non-Premarin preparations among my 195 patients in London and eventually decided, based upon my patients' success with non-Premarin preparations, to abandon the use of Premarin except in that small group of women back home in New Haven who seemed to be doing well with the drug.

47. As recent events show, despite all the years in which it has been available, significant questions remain regarding both Premarin's safety and its efficacy. Most significantly, the WHI discontinued its study of Premarin after finding that estrogen had no effect on heart disease, had an increased risk for stroke and, possibly, dementia (while decreasing the risk of hip fracture).

48. Unfortunately, many women and their physicians have lost their trust in hormone therapy as a result of the WHI findings. Many of those who continue to believe in the benefits of hormone therapies for postmenopausal women have sought Cenestin, as representative of a modern and more effective treatment.

VII. The Impact of Formulary Obstacles on Physician Prescribing Habits

49. Physicians have the right and duty to use the most effective and safest drugs available, and to prescribe those medications which, in their professional judgment, are best for their patients. There is a natural learning curve in administering drugs that enables the physician to tailor a therapy to individual needs and to achieve optimal results. To do so, however, the physician must be able to choose and obtain the drugs that are best for their patients without undue restrictions.

50. The availability of prescription drugs is directly affected by managed care policies, and specifically by the formulary policies instituted by health maintenance organizations (HMOs) and pharmacy benefit managers (PBMs). For the past 33 years I have worked as an attending physician in Yale University Health Services, an HMO, in which I have been free to obtain the drugs and dosage forms I wish for my patients. However, as I have traveled the country and talked with other physicians, I have come to learn that this freedom of choice is far from universal.

51. Many, if not most, of the physicians I have spoken with are effectively limited to the drugs that are listed on the formularies of their managed care pharmacies – often to the exclusion of more effective and safer drugs. When non-formulary alternatives are allowed, there usually is a process requiring a formal request and approval by the pharmacy review board of the managed care organization. For many physicians, already time-stressed by the demands of current-day medical practice, the frequent result is that the "path of least resistance", *i.e.*, prescription of the drug already on formulary, is taken rather than prescription of a non-formulary drug.

52. Additionally, for some physicians, who may be unfamiliar with the full process by which drugs come to be listed on formularies, the fact that a particular drug is listed on the formulary may serve as a stamp of approval for a drug – when, in reality, it may simply reflect the fact that the drug manufacturer and the HMO or PBM have agreed to a contract that effectively restricts other drugs' access to the formulary.

53 Even physicians who are determined to provide a non-formulary alternative to their patients may face an uphill battle. For example, for more than a decade, I and other researchers have been presenting a compelling argument that natural progesterone, approved by the FDA and demonstrated to be safe and effective in an important National Institutes of Health research

study, should be the first choice when adding a progestogen to hormone therapy. Nevertheless, formularies throughout the country carried Provera (MPA), and required physicians to go through the special request process if they wished their patients to receive the natural progesterone product, Prometrium. Most often, the patients had to purchase and pay for the progesterone on their own.

58. However, in two communities (Madison, Wisconsin and Poughkeepsie, New York), where I have taught about the advantages of progesterone over MPA, physicians mounted an effort to overcome the formulary restrictions against Prometrium, eventually winning the battle in both places. It took more than two years and the occurrence of adverse effects from MPA (*e.g.*, stroke) to accomplish a change, but physicians eventually were able to overcome the formularies' resistence and have Prometrium placed on the list of readily available drugs.

59. Physicians with an increased awareness of the problems and questions raised by their patients' use of Premarin need and want better treatments for the women who are suffering from the effects of menopause-related hormone deficiency. I am aware today of an increasing number of very busy medical practitioners across the country whose clinical experiences and increased knowledge and information have led them in the last two to three years to almost entirely replace Premarin prescriptions with alternative treatments, including Cenestin.

60. My over forty-one years of experience treating menopausal patients has confirmed in my own mind that alternative treatments such as Cenestin are superior methods for alleviating the symptoms experienced by women during menopause.

Dated April 22, 2004

Philip M. Sarrel, M.D.